National Marrow Donor Program®

Entrusted to operate the
C.W. Bill Young
Cell Transplantation Program

National Coordinating Center
3001 Broadway St. N.E.
Suite 100
Minneapolis, MN 55413-1753

Toll Free: 1 (800) 526-7809
Phone: (612) 627-5800
marrow.org

February 10, 2009

Cdr. Elizabeth Montcalm-Smith
Office of Naval Research (ONR 342)
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: **Quarterly Performance/Technical Report of the National Marrow Donor Program®**

Reference: Grant Award #N00014-06-1-0058 between the Office of Naval Research and the National Marrow Donor Program

Dear Cdr. Montcalm-Smith:

Enclosed is subject document which provides the performance activity for each statement of work task item of the above reference for the period of October 1, 2008 to December 31, 2008.

Should you have any questions as to the scientific content of the tasks and the performance activity of this progress report, you may contact our Chief Medical Officer – Dennis L Confer, MD directly at 612-362-3425.

With this submittal of the quarterly progress report, the National Marrow Donor Program has satisfied the reporting requirements of the above reference for quarterly documentation. Other such quarterly documentation has been previously submitted under separate cover.

Please direct any questions pertaining to the cooperative agreement to my attention (612-362-3403 or at cabler@nmdp.org).

Sincerely,

Carla Abler-Erickson

Carla Abler-Erickson, MA
Sr. Contracts Representative

Enclosure: Quarterly Report with SF298

C: D. Ivery – ACO (ONR-Chicago), letter and enclosure
Dr. Robert J. Hartzman, CAPT, MC, USN (Ret): letter and enclosure
Jennifer Ng, PhD – C.W. Bill Young Marrow Donor Recruitment and Research Program, letter and enclosure
J. Rike - DTIC (Ste 0944): letter and enclosure
NRL (Code 5227): letter and enclosure
Dennis Confer, MD, Chief Medical Officer, NMDP, letter only
Michelle Setterholm, NMDP letter only

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
10-02-2009	Quarterly	Oct – Dec 2008

4. TITLE AND SUBTITLE
Quarterly Performance / Technical Report

5a. CONTRACT NUMBER
N/A

5b. GRANT NUMBER
N00014-08-1-0058

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)
Setterholm, Michelle

5d. PROJECT NUMBER
N/A

5e. TASK NUMBER
Project 1, 2, 3, 4

5f. WORK UNIT NUMBER
N/A

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
National Marrow Donor Program
3001 Broadway St., N.E., Ste. 500
Minneapolis, MN 55413

8. PERFORMING ORGANIZATION REPORT NUMBER
N/A

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Office of Naval Research
875 N. Randolph St.
Arlington, VA 22203

10. SPONSOR/MONITOR'S ACRONYM(S)
ONR

11. SPONSORING/MONITORING AGENCY REPORT NUMBER
N/A

12. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited

13. SUPPLEMENTARY NOTES
N/A

14. ABSTRACT

1. Contingency Prepardness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors : Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenetic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation**:** Create a platform that facilitates multicenter collaboration and data management.

15. SUBJECT TERMS
Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE	Same as Report	27	Dennis L. Confer, MD – Chief Medical Office
U	U	U			19b. TELEPONE NUMBER (*Include area code)* 612.362.3425

NATIONAL MARROW DONOR PROGRAM®

Creating Connections. Saving Lives.™

Grant Award N00014-08-1-0058

QUARTERLY
PERFORMANCE / TECHNICAL REPORT
FOR
OCTOBER 01, 2008 to DECEMBER 31, 2008

Office of Naval Research

And

The National Marrow Donor Program
3001 Broadway Street N.E.
Minneapolis, MN 55413
1-800-526-7809

QUARTER PROGRESS REPORT

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

October 01, 2008 through December 31, 2008

TABLE OF CONTENTS

IIA. Contingency Preparedness – Hypothesis 1: Recovery of casualties with significant myelosuppression following radiation or chemical exposure is optimal when care plans are designed and implemented by transplant physicians	
IIA.1.1 Aim 1: Secure Interest of Transplant Physicians	**Period 4 Activity:** • During 2008 a total of 826 center staff successfully completed the Basic Radiation Training (BRT); as of December 31, 2008 a total of 1,621 certificates of training had been issued for completion of BRT; this resulted in a passing rate exceeding 95%. • During this period we continued planning for a 2009 advanced training course for RITN centers to send staff to. The course is titled Advanced Radiation Medical Emergency training course and conducted in Oakridge, TN at the Radiation Emergency Assistance Center/Training Site (REAC/TS). Class will be held on March 26 & 27, 2009. Course lessons include: o Basic Health Physics & Radiation Protection: Part I o A History of Serious Radiological Incidents: The Real Risk o Health Physics & Contamination Control: Part II o Radiation Detection, Monitoring & Protection Laboratory Exercise & Quiz o Diagnosis & Management of the Acute Radiation Syndrome (ARS) o Diagnosis & Management of Internal Contamination o Diagnosis & Management of Acute Local Radiation Injury & Case Review: Yanango Peru o Radiation Sources & Radiological Terrorism o Radiation Emergency Area Protocol Demonstration o Radiation Emergency Medical Management Drill o Radiation Dose Estimations – Problem Solving Session • During this period we initiated planning for the 2009 RITN conference "Nuclear Terrorism: Hematology/Oncology Center Preparedness" to be held in Bethesda, MD on May 18th (additional details of this conference are listed under AIM II A 2.1).
IIA.1.2 Aim 2: GCSF in Radiation Exposure	**Period 4 Activity:** • No activity this period.

IIA.1 3 Aim 3: Patient Assessment Guidelines and System Enhancements	**Period 4 Activity:** In October STAR Link version 5.12 was released to support the Navy contingency project. • Health History Questionnaire (HHQ) **–** An electronic version of the entry of The DR/Prelim HHQ will be available. • Communications History - A new section has been created in STAR Link that will show automated communication. **Do It Yourself (DIY)** application efforts were focused on simple project enhancements and preparation for the Navy Contingency project. Discussions were held with IT staff on how to incorporate logic into the STAR suite of software to improve donor identification after a disaster. • **Statistic:** DIY Online Donor Registration through www.marrow.org resulted in a **total of 15,000** between 1/1/08 – 12/31/08.
IIA 1.4 Aim 4: National Data Collection Model	**Period 4 Activity:** • FormsNet v2.6.3 and v2.6.4 and v2.7.0 were released during the previous quarter including a number of bugfixes and enhancements including improved forms due and randomization rules. New forms were added and several minor bugfixes and enhancements were implemented. • AGNIS was updated to allow submission of all of the core forms for the CIBMTR mandated by the SCTOD (registration, pre-TED, TED, HLA, IDM, Infusion and Death). The data curation effort to register all 11,000 data elements in the caDSR continues to make progress. A new curator staff position was added and the model for curation (and therefore AGNIS messages and databases) was extended to include “modules” which will reduce the overall effort of curation by 10-20%.

IIA. Contingency Preparedness – Hypothesis 2: Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation.	
IIA.2.1 Aim 1: Contingency Response Network	**Period 4 Activity:** • Closed out the FY08 agreement for the Radiation Injury Treatment Network (RITN) o 96% (49) of the 51 RITN centers completed all of the required tasks for payment in accordance with the participation agreement. ▪ Centers that did not complete all of the required tasks were not compensated for their participation in RITN. o Annual running trend of this metric is: FY06 - 92% | FY07 - 96% | FY08 - 96% • Distributed FY09 RITN participation agreements to all 51 centers and formally invited six (6) additional transplant centers to participate in RITN. All have verbally agreed to participate and their signed participation agreements are under review by their legal teams: o Vanderbilt University in Nashville, TN o CHORI in Oakland, CA o Karmanos Cancer Center in Detroit, MI o Mayo Clinic in Rochester, MN o Mayo Clinic in Phoenix, AZ o City of Hope in Phoenix, AZ • During this period we initiated planning for the 2009 RITN conference "Nuclear Terrorism: Hematology/Oncology Center Preparedness" to be held in Bethesda, MD on May 18, 2009. o We are planning for 200 attendees (a slight increase from the 2007 conference attendance) o This conference will have a group session in the morning to provide a common operating picture then have three (3) interactive breakout workshops held three (3) times in the afternoon so that all attendees have the opportunity to participate.

- Morning sessions include:
  - Threat Scenario Overview
  - National Disaster Medical System
  - Medical response expectations 10, 100, 1,000 miles from epicenter
  - Altered Standards of Medical Care Overview
  - NMDP Planning and data collection
- Afternoon interactive breakout workgroups include:
  - Altered Standards of Care
  - Logistical issues – bed mgmt, use of non-hospital loc, & staffing issues
  - Provision of medical care – early and late care
- The conference will culminate with a report of findings by the afternoon session moderators, with the intent of publishing these findings later in the year.

- Meetings:
  - Conducted three (3) monthly conference calls with RITN centers to assist in completion of required tasks and to improve integration into the network.
  - Initiated planning for a RITN Steering Committee meeting to be held during the 2009 ASBMT/CIBMTR Tandem meetings on February 11, 2009, the meeting agenda consists of:
    - Opening remarks:
      - Roundtable introductions
      - RITN accomplishments in 2008
      - 2009 expansion of RITN
      - 2009 RITN tasks and educational activities
      - New developments
    - RITN Tabletop Exercises Lessons Learned from 2006-2008 and a 2009 Tabletop Exercise Overview
    - Maintaining RITN's Momentum

	▪ Medical Reserve Corps Overview • Distributed three (3) "Rad in the News" open source news summary reports to RITN centers and partner organizations with the intent to maintain awareness of international activities related to radioactive materials. • Presented "Overview of the Radiation Injury Treatment Network" at the AABB annual meeting in Quebec, Canada. • Initiated the development of the 2009 RITN Tabletop Exercise: o This year's tabletop exercise will require more involvement from RITN centers than in the past. o In addition to tougher questions centers will be asked to document how they will respond to certain scenarios.
IIA.2.2 Aim 2: Sibling Typing Standard Operating Procedures	**Period 4 Activity:** • Discussed with appropriate IT staff how to incorporate sibling typing into future developments of Traxis or the STAR suite of software • A pilot project was initiated with one laboratory to evaluate high volume, high resolution, rapid HLA typing to support a contingency event. A pretest of 20 samples was typed and 100% of the HLA results were accurate and reported within 7 days. Eighty-nine new volunteer donors and 3 quality control samples will be tested weekly for 12 weeks and results will be reported within 7 days. Typing resolution, quality, TAT and number of repeats will be monitored each week and a summary provided at the end of three months. At that time, a decision will be made for increasing to higher volumes.
IIA. Contingency Preparedness – Hypothesis 3: NMDP's critical information technology infrastructure must remain operational during contingency situations that directly affect the Coordinating Center.	
IIA.3.1 Aim 1: I.S. Disaster Recovery (DR)	**Period 4 Activity:** • Completed partial retro fit of coordinating center server room to prepare for disaster recovery test. Have begun planning for the test which will be conducted in 2nd quarter of FY 2009.

IIA.3.2 Aim 2: Critical Facility and Staff Related Functions	**Period 4 Activity:** • **Business Continuity Planning:** o Emergency communications: ▪ Satellite telephone connectivity issues continue to cause problems at all RITN center locations. Since Global Star satellite phone service could not provide a defined path to reliable future communications we replaced the telephones with Iridium portable satellite telephones. ▪ Conducted a communications test with the NMDP Network via by email notification, tested notifying NMDP staff and key partners via the telephonic Emergency Notification System, tested the Coordinating Center public announcement system and the GETS cards. o Conducted business continuity site visits to two (2) NMDP operated donor centers. Distributed Business Continuity Action Guides, reviewed procedures in place, and discussed methods to improve preparedness at each location. o Continued to develop a business continuity plan to improve the resiliency of the organization immediately following a catastrophic incident impacting the NMDP Coordinating Center. o Initiated planning with IT staff to conduct a staff business continuity exercise where staff will perform key work duties from a remote work environment.
IIB. Rapid Identification of Matched Donors – Hypothesis 1: Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection.	
IIB.1.1 Aim 1: Increase Registry Diversity	**Period 4 Activity:** In the process of reviewing the HLA override reports, it was discovered that many African American (AFA) adult volunteers typed prior to 1994 as DRB1*1501 were actually DRB1*1503. HLA-DRB1*1503 was initially described in 1992, but HLA testing kits did not routinely include probes to distinguish DRB1*1501 and *1503 until 1994. An HLA typing project was conducted to confirm whether the DRB1*1501 typing listed for the AFA donors tested prior to 1994 was actually DRB1*1503.

	Two hundred and forty nine AFA samples were retyped and 25% of the initial DRB1*1501 results were found to be correct (66 of 265 results). In addition, HLA-A and –B typing was repeated on a subset of the cohort previously tested using serological methods. After retyping, a discrepancy rate of 4.9% and 8.5% was uncovered for HLA-A and B, respectively. This project highlights the importance of technical oversight of the data and the necessity to upgrade typings routinely in order to provide the most accurate HLA data for searching patients. Five contracted HLA testing laboratories performed HLA-A, B, DRB1 typing, one laboratory performed HLA-A, B, C, DRB1 typing, on a total of 38,926 newly recruited donors o Blind quality control testing error rate was 0.29%, meeting the project requirement of ≤ 2.0%. o On-time testing completion rate was 98%, meeting the project requirement of a minimum of 90% of typing results reported within 14 days of shipment of samples. To successfully serve all patients in need of cellular transplantation, the Marketing and Communications Department continued to focus on developing and executing strategies and tactics that increase awareness and engagement among target audiences. During October – December, 2008, in support of this strategy we reprinted English and Spanish language versions of our primary educational tool *Life it's in You* brochure; developed a New Registry Member Exit card which reinforces key messages to help increase donor availability; and reprinted the donor self-deferral card and multi-race recruitment sheet.
IIB.1.2 Aim 2: Evaluate HLA-DRB1 High Res typing	**Period 4 Activity:** • This task is closed.
IIB.1.3 Aim 3: Evaluate HLA-C Typing of Donors	**Period 4 Activity:** • This task is closed.

IIB.1.4 Aim 4: Evaluate Buccal Swabs	**Period 4 Activity:** The Sample Storage Research Study (SSRS) began in September, 2007. The first time point (Time Point Zero) for donor sample evaluation was September, 2007. The second time point (Time Point 1 Year) was September, 2008. A preliminary analysis of the results submitted in October, 2008 indicated that all three sample types – frozen blood, blood spotted onto filter paper, and buccal swabs – were HLA typed with 100% accuracy. An analysis of the DNA quality is pending. The first time point (Time Point Zero) for Quality Control (QC) swab evaluation was December, 2007, the second time point (Time Point 6 months) was June, 2008, and the third time point (Time Point 12 months) was December, 2008. A preliminary analysis of the results submitted in January, 2009 show all samples were HLA typed with 100% accuracy.
IIB 1.5 Aim 5: Enhancing HLA Data for Selected Donors	**Period 4 Activity:** This aim consists of two prospective, registry-based typing projects, which have the potential to strategically identify and improve the HLA typing and availability of donors most likely to match searching patients from domestic TCs. The primary goal of the Replacement Donor Pilot Study was to identify an HLA-A, B, DRB1 identical replacement donor for every donor selected for workup by a TC. • While the study was completed in December 2007, the NMDP staff continued to monitor the patient-directed utilization of donors typed in this project. The primary objective of the Optimum Donor Pilot Study was to develop a systematic strategy to classify adult donors into phenotype categories based upon the likelihood to appear on a patient's search. Adult donors with high potential to match searching patients were selected and proactively contacted to verify availability, upgrade HLA, and/or secure additional stored samples in an effort to increase their utilization and to help reduce the search times for patients. • Approximately 450 donors were selected and samples shipped for prospective HLA typing during this reporting period. NMDP staff continues to monitor the patient-directed utilization of all donors typed through the project.

	• Donor selection strategies were extended to include pilot strategies for the search for potentially matching HLA-A, B only (4 of 4) typed donors for patient phenotypes without a potential 6 of 6.
IIB 1.6 Aim 6: Maintain a Quality Control Program	**Period 4 Activity:** • No activity this period.
IIB. Rapid Identification of Matched Donors – Hypothesis 2: Primary DNA typing data can be used within the registry to improve the quality and resolution of volunteer donor HLA assignments.	
IIB 2.1 Aim 1: Collection of Primary Data	**Period 4 Activity:** • Two new minor versions of HML (0.3.2 and 0.3.3) were developed during the past quarter to allow more flexible reporting of SBT as a primary and secondary (ambiguity resolution) method. Testing has continued steadily with two NMDP contract labs to report data in the new format. • The first KIR SSO probe kit was registered. Messages from laboratories reporting data under the donor-recipient pairs project for KIR at "intermediate resolution" have been tested.
IIB 2.2 Aim 2: Validation of Logic of Primary Data	**Period 4 Activity:** • This task is closed.
IIB 2.3 Aim 3: Reinterpretation of Primary Data	**Period 4 Activity:** • This task is closed.
IIB 2.4 Aim 4: Genotype Lists & Matching Algorithm	**Period 4 Activity:** • No activity this period.

IIB. Rapid Identification of Matched Donors – Hypothesis 3: Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor.	
IIB.3.1 Aim 1: Phase I of EM Haplotype Logic	**Period 4 Activity:** • Two abstracts were presented at the annual ASHI meeting that utilized data from EM haplotype analysis "**Association of HLA-B with Common HLA-C Alleles Identical within antigen recognition site (ARS) in Minority Populations"** and **"HLA-B*0705 and B*0706 Occurrence and Association Data in Minority Donors".**
IIB 3.2 Aim 2: Enhancement of EM Algorithm	**Period 2 Activity:** • Several abstracts were presented at the ASHI meeting including 3 posters: "Characteristics Affecting Donor Selection in the NMDP Registry", "Recovery of ancestral Latino population founders using high resolution HLA haplotypes" & "Anthropological Insights from a Novel Visualization and Clustering Tool for HLA Haplotypes and Populations". One abstract that was accepted for oral presentation, "Discerning KIR haplotypes" won the ASHI Scholar Award. • Two of these abstracts were also presented at the ASHG (American Society for Human Genetics) meeting along with abstract analyzing Brazilian HLA haplotypes in comparison to US. • Analysis is continuing on the Israel and Mexican American HLA frequency manuscripts.
IIB 3.3 Aim 3: Optimal Registry Size Analysis	**Period 2 Activity:** • HLA typing was completed for the random pool CAU (European American) donors. These typings, along with a previous cohort of AFA (African American) donors will be utilized for measuring the "actual" 8/8 and 7/8 allele match rates. Two abstracts utilizing these data were presented at the 2008 ASHI meeting "**DQB1/DRB1 Associations by Race for CWD DQB1 Antigen Recognition Site (ARS) Identical Alleles" and "DRB1*1401/*1454 Haplotype and Association Vary by Race**" and " • A report summarizing the current activity developing registry matching models was developed including the results of a number of computer simulations that explored the effect of sample-

	generating population size on the match rates using the current registry modeling approach.
IIB 3.4 Aim 4: Target Under-represented Phenotypes	**Period 2 Activity:** • A report was developed comparing a number of different strategies for mapping HLA types geographically. Initially this involves showing heat-maps of HLA genotypes for existing donors but the same mapping strategy will be applied to geographically encode expected genotypes based on haplotype frequencies. • The geographical information system developed for work under this aim has been used to generate a number of ad hoc reports for the recruitment area based on donor demographics and donor center location such as "median drive time".
IIB 3.5 Aim 5: Bioinformatics Web Site	**Period 4 Activity:** • This task is closed.
IIB 3.6 Aim 6: Consultants to Improve Algorithm	**Period 4 Activity:** Funding on this aim provides support for the Search Strategy Advice (SSA) program provided to TCs to meet their need for HLA expertise for donor selection. The program includes external and internal HLA experts who review each patient search and write a report summarizing a search strategy to assist the TC in rapidly identifying the best potential stem cell source for their patient. The HLA experts provided valuable feedback for algorithm and IT enhancements throughout the quarter. The SSA program completed 385 patient reports for 75 TCs during this quarter. The average turnaround time for all reviews was 4.1 business days which exceeded the program requirement of 5 business days. Both internal and external experts participate in a rigorous QC program and all met the requirements during the past quarter.

IIB. Rapid Identification of Matched Donors – Hypothesis 4: Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.	
IIB.4.1 Aim 1: Expand Network Communications	**Period 4 Activity:** **STAR2 Application Upgrade** • To aid the Search and Transplant Department in maintaining patient safety, we deployed functionality to improve reliability of persisting typings for new donors. • To increase the reliability and timeliness of notifying members of search activity, we deployed functionality to improve reliability in sending data to member centers. This was done by improving error handling of transaction delivery client.
IIB.4.2 Aim 2: Central Contingency Management	**Period 4 Activity:** Central Contingency Management uses trained NMDP coordinating center staff to provide comprehensive donor/cord selection recommendations and patient search monitoring for TC staff. Navy funds support the expansion of the Central Search Support (CSS) service for contingency management. During the quarter the NMDP continued efforts to expand this service to additional transplant centers. Two transplant centers had trial patient cases facilitated. NMDP staff distributed information on the CSS service to several transplant centers following inquiries about the program. The continued expansion of CSS increases the NMDP's capabilities to provide centralized rapid turnaround search support in the event of a contingency event.
IIB.4.3 Aim 2: Benchmarking Analysis	**Period 4 Activity:** • This task is closed.

IIB.4.4 Aim 2: Expand Capabilities of Collection and Apheresis Centers	**Period 4 Activity:** In 2008, NMDP contracted with American Healthcare Solutions (AHS) to assess ways in which the NMDP would increase availability and accessibility of product collection centers (Apheresis Centers and Marrow Collection Centers). AHS subcontracted the bulk of the project to Life Science Strategy Group (LSSG), who completed Phase IIa of the project in Q1 of FY2009. LSSG (two people) conducted a 2-day workshop on-site at the NMDP office in Minneapolis on September 22/23, 2008. The workshop involved NMDP staff from multiple departments, as well as two Apheresis (AC) and Collection Center (CC) coordinators from NMDP sites in California and New Jersey. The objective of the workshop was to qualitatively assess six strategies (previously vetted by a core group of NMDP staff) to prioritize and to determine which four of the six should continue in the analysis for further consideration. The assessment involved approximately two hours of discussion on each strategy to consider issues, pros, cons, feasibility and potential costs. LSSG used the results of this workshop to prepare a report for Phase IIa that summarized their work and the group's conclusions. The six strategies assessed are listed below, with strategies 1-4 being those that progressed to Phase IIb with LSSG. 1. Web-based Scheduling for product collections 2. DC/AC/CC Tiering 3. AC/CC Recognition and Incentive Program 4. Payment for AC/CC Collection Coordination 5. Standardization of DC/AC/CC Procedures of Interaction 6. Review NMDP Product Cryopreservation Policy.

IIC. Immunogenetic Studies – Hypothesis 1: HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations it will not be possible to delay transplant until a perfectly matched donor can be found.	
IIC.1.1 Aim 1: Donor Recipient Pair Project	**Period 4 Activity:** In 1994 a retrospective Donor/Recipient Pair HLA typing project to characterize class I and class II alleles of donor/recipient paired samples from NMDP's Repository was initiated. The goals of this ongoing research project are to assay the impact of DNA-based HLA matching on unrelated donor transplant outcome, develop strategies for optimal HLA matching, evaluate the impact of matching at alternative HLA loci on transplant outcome and finally to promote the development of DNA-based high resolution HLA typing methodologies. • Sample Group 20 (SG20) period of performance came to a close on August 31, 2008. During this quarter discrepancy, no make and linkage analyses were completed. 490 pairs (98%) of SG20 were audited and made available for research. • The project period for SG21 began September 1, 2008 and came to a close on December 31, 2008. The contracts for SG21 (500 pairs) testing included intermediate and high resolution HLA and also presence/absence testing for 14 KIR loci (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1). • SG22 consisting of 274 pairs will begin early next quarter with a project period from January 5, 2009 to April 31, 2009. The testing strategy is the same as for SG21.
IIC. Immunogenetic Studies – Hypothesis 2: Even when patient and donor are HLA matched, GVHD occurs so other loci may play a role.	
IIC 2.1 Aim 1: Analysis of non-HLA loci	**Period 4 Activity:** In 2005 a pilot study to perform high resolution KIR gene typing was launched. The primary objectives of the study were to move technology forward from the current practice of locus level typing to high resolution typing, disseminate information and protocols in an open source mechanism and develop reference lines for use in individual laboratories. • Resolution of new alleles found within Phase 1, 2 and 3 of the KIR Typing Pilot project was

	discussed with the DNA Project Officer and a strategy for resolution is under development. • An abstract entitled, "Discerning KIR Haplotypes" was presented and received the ASHI Scholar Award at the ASHI 2008 meeting in Toronto, Canada on October 28, 2008. The Immunobiology Project Results (IPR) database and its applications will allow for storage and analysis of all immunogenetic data collected on NMDP research samples. This database will replace the existing HLA donor/recipient pairs database and facilitate storage and analysis of data from other immunogenetic loci (KIR, microsatellites, single nucleotide polymorphisms, etc). • The Scientific Services and Bioinformatics departments continued to collaborate on the design and development of the IPR database application and tools. • A software-developer contractor completed the initial development for the acceptance, validation, and storage of incoming HLA and KIR typing data via Histoimmunogenetics Markup Language (HML), including genotype lists. The next phases will test this development and implement the reporting functionality. They are scheduled for completion next quarter. • Another software-developer contractor implemented a web-browser-based application which allows users to view typing results as stored in the database. • A third contractor worked on an application to transfer data from the existing legacy database to IPR. It is scheduled for completion next quarter.
IIC 2.2 Aim 2: Related Pairs Research Repository	**Period 4 Activity:** Related transplant research sample collection continued with a pilot project initiated at seven TCs in December 2007. At the end of the current quarter, 367 samples (164 donor/recipient pairs) had been submitted to the Repository. A programmer finished development of the Research Sample Repository Tools suite to facilitate management of samples. Enhancements to the tools will be tested and released to production next quarter. In August of 2008 a pilot study was launched to evaluate the use of whole genome amplification (WGA) on repository samples as a potential replacement of B-LCL transformation as a renewable source of DNA for research. The pilot evaluated the potential use of all repository sample types stored for differing lengths of time as a source of genomic DNA for the WGA process. Following WGA, the amplified DNA samples

	were high resolution typed at HLA- A, B, C, DRB1, DQB1, and DPB1 by SBT. The purpose of this testing was to validate the effectiveness and reliability of WGA at producing unbiased, high quantity and quality DNA products. • This testing was performed on 5 samples of each of the following types: o PBMC stored in liquid nitrogen (LN2) o PBMC stored at -80º C o Granulocytes stored at -80º C o BLCL stored in LN2 o BLCL stored at -80º C o Whole Blood stored in LN2 o Whole Blood stored at -80º C o Filter Paper stored at room temperature (RT) o Buccal Swabs stored at RT • Initial extraction of genomic DNA resulted in varying quantities of product based on sample type. After WGA was performed all samples achieved amplification close to the expected amount of 40ug from an initial input of 10ng. • The HLA typing results on the WGA DNA from PBMC, granulocytes, BLCL and whole blood were 100% concordant with the previous typing. The typing of WGA DNA from buccal swabs and filter papers proved problematic for some alleles resulting in prevalent weak SBT signals, high SBT backgrounds, and no achievable typing. The use of WGA appears to be plausible using repository samples other than buccal swabs and filter papers. An evaluation of cord research samples will be completed next quarter.
IID. Clinical Research in Transplantation – Hypothesis 1: Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.	
IID.1.1 Aim 1: Observational Research, Clinical Trials and NIH	**Period 4 Activity:** The Cord Blood Research sub-Committee met monthly to discuss study priorities and plan analyses. Activity during the past quarter focused on the following areas:

Transplant Center	• Prepared and supported development of several well attended and received Cord Blood related sessions at the 2008 NMDP Council meeting o A workshop entitled, "CFU Methodologies: Considerations in Practice Standards and Outcome Variability", that will cover issues related to the current CFU assay systems and new procedures designed to minimize interlab variability. o A workshop entitled, "New Frontiers in Cord Blood Processing", that will provide an overview of cord blood processing methodologies and systems. o A wet lab for cord blood bank technicians focused on best practices for CFU assay setup and enumeration. • Continued work on several research projects o A study was initiated to evaluate differential cellular recoveries for CBUs from various race groups with a focus on determining root causes of low cell yields from African American CBUs. MD Anderson Cancer Center, Duke and the St. Louis Cord Blood Bank compiled the results of pre and post processing cell yield s for CBUs from various racial/ethnic groups. The subgroup met at Council Meeting to compare the preliminary results. o The cell processing laboratory at Memorial Sloan-Kettering recently developed a modified gating strategy for CD34 viability assessment that correlates with engraftment potential in a single center study. MD Anderson initiated a pilot study to assess the feasibility of using the gating strategy on archived flow cytometry files. If successful, the committee will develop and perform a retrospective analysis of recent transplants. o The Duke laboratory initiated a pilot project to evaluate various assay systems for CBU potency assessment prior to transplantation. The preliminary results were presented at the HRSA advisory council meeting in December. The Committee will use the results to develop a multicenter study to extend the analysis. o A committee subgroup met at the 2009 ASH meeting to develop a CIBMTR protocol for a retrospective observational study of single versus double cord blood transplants in adult patients. The protocol was submitted to the CIBMTR Graft Sources Working Committee for review and will be presented during the BMT Tandem meeting next quarter.

Observational Research

- Staff continued work on various observational studies within the area of Immunobiology and GVHD.
- A total of 6 abstracts were presented at the 2008 ASH meetings; three posters and 3 oral presentations.
- One manuscript from the GVHD Working Committee was published during this reporting period.

Prospective Studies; RCI BMT

- Activity related to the BMT CTN PBSC vs. Marrow trial continued with a total of 483 donor/patient pairs randomized at the end of this reporting quarter. Accrual at the end of September was 88% complete. We continue to see an increase in work-ups and randomizations which directly reflects efforts made to increase accrual and the goal of completion in 2009.
- Adult Double Cord trial activity during this period included the activation of an additional site for a total of 9 sites open to accrual. Four patients were enrolled during this quarter for a total of 11 patients giving us a 20% completion rate. Staff coordinated and completed monthly PI and coordinator calls.
- Revlemid trial activity continued to progress forward. During this reporting period the database was finalized and site initiations were completed for four centers. Final IRB approvals were received from five centers during this period. It is expected that a minimum of two sites will be open to accrual by the end of the next reporting period.
- Activity continued on protocol development for the AZA study titled *Low Intensity Therapy of MDS Prior to Non-Ablative Allogeneic Stem Cell Transplantation.* Additional funding continues to be explored to support portions of this study.

Work began on a requirements document for the FormsNet platform development to support donor data management and clinical trial management.

IID.1.2 Aim 2: Research with NMDP Donors	**Period 4 Activity:** • Staff continued support of a Donor Ethnicity study with Dr. Galen Switzer from the University of Pittsburgh. • Staff continued to collaborate on a COG KIR study. Activities include facilitating the collection of a donor blood sample and shipment to the study lab. To date, 11 patients have been enrolled which equates to 51 donor sample requests being facilitated. • Staff continued to develop a protocol for centralizing the NMDP long-term donor follow-up. It is expected that the protocol will be submitted for approvals spring 2009. • Staff continues to work on logistical details for obtaining donor samples to support a study assessing use of allogeneic cytotoxic T-lymphocytes in children with acute leukemia.
IID.1.3 Aim 3: Expand Immuno-biology Research	**Period 4 Activity:** The CIBMTR IBWC met monthly during the quarter to discuss progress on ongoing research studies • Five abstracts were submitted and accepted for presentation at the 2009 Tandem BMT meetings: o S Arai, D Tyan, T Vayntrub, S Vail, A Hassebroek, C Brady, S Spellman, DMiklos. **Antibodies are detected against mismatched HLA class II alleles and not class I following allogeneic hematopoietic cell transplantation.** Accepted for poster presentation. o B Sahaf, B Narasimhan, K Miller, K Spencer, S Spellman and D Miklos. Female **Donor H-Y Seropositivity Does not Predict Male Recipient HCT outcomes, including cGVHD**. Accepted for poster presentation. o J Venstrom, T Gooley, S Spellman, R Hasan, J Pring, M Malkki, B Dupont, E Petersdorf, K Hsu. **Donor KIR 3DS1 is associated with Less Acute GvHD Following Unrelated Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies.** Accepted for oral presentation. o S Cooley, P Parham**,** E Trachtenberg, , X Luo, C Le, J Klein, S Marsh, D Weisdorf, and J Miller. **The Relapse-free Survival Benefit Associated with Group B KIR Haplotype Donors for Unrelated Hematopoietic Cell Transplantation is Unique to Acute Myelogenous Leukemia.**

Accepted for oral presentation and recipient of a best abstract award.

- P Shaw, F Kan, K Ahn, S Spellman, S Davies, M Pulsipher, E Petersdorf, J Klein, S Lee and Others on behalf of the writing committee. **Pediatric BMT for Malignancy Using Zero/One Antigen Mismatched Family Donors or Unrelated Donors Have Similar Outcomes, Both of which are Inferior to Matched Sibling Donors.** Accepted for oral presentation and recipient of a best abstract award.

- Three abstracts were submitted to the 2009 EBMT meeting:
  - M Stern, A Gratwohl, M Malkki, Y Morishima, S Spellman, T Gooley, E Petersdorf on behalf of the International Histocompatibility Working Group in Hematopoietic Cell Transplantation. **HLA-DR15 and Outcome of Unrelated Donor Hematopoietic Stem Cell Transplantation – An IHWG Analysis.** Submitted.
  - B Shaw, E Petersdorf, T Gooley, M Malkki, K Fleischhauer, S. Spellman, Y Morishima, E Zino. **Significant differences in outcome following unrelated donor HCT can be better predicted using an algorithm incorporating both allele and epitope level matching for HLA-DPB1.** Submitted.
  - Z Shamim, L Ryder, M Haagenson , S Spellman, T Wang, S Lee, K Müller. **Polymorphism in the genes encoding human interleukin-7 Receptor-alpha (IL-7Ra) and outcome after allogeneic hematopoietic cell transplantation (HCT) with matched unrelated donor (MUD)**. Submitted.
- IBWC staff and principal investigators prepared posters and slides for six ASH abstract presentations.
- Ten new proposals were received and subjected to a preliminary review by the IBWC leadership to assess feasibility. 7 of the proposals were deemed feasible and will be discussed at the IBWC meeting during the BMT Tandem Meetings next quarter for approval and prioritization by the full committee.

Funding for CIBMTR IBWC studies:

- Research funds supported development of a prospective research sample collection protocol for a

	study of cGVHD in long-term surviving male recipients who received HSCT from female donors. Potential study subjects received mailings to solicit participation last quarter. Prospective blood samples were submitted by 17 of 28 consented participants. Collection from the remaining participants should be completed in the next quarter.

ACRONYM LIST

AABB	American Association of Blood Banks	IDM	Infectious Disease Markers
AC	Apheresis Center	IHWG	International Histocompatibility Working Group
AHS	American Healthcare Solutions	IND	Investigational New Drug
AML	Acute Myelogenous Leukemia	IS	Information Services
ARS	Acute Radiation Syndrome (also known as Acute Radiation Sickness)	IT	Information Technology
ASBMT	American Society for Blood and Marrow Transplantation	IRB	Institutional Review Board
ASHI	American Society for Histocompatibility and Immunogenetics	KIR	Killer Immunoglobulin-like Receptor
B-LCLs	B-Lymphoblastoid Cell Lines	LN2	Liquid Nitrogen
BMT CTN	Blood and Marrow Transplant - Clinical Trials Network	LSSG	Life Science Strategy Group
BRT	Basic Radiation Training	NCI	National Cancer Institute
C&A	Certification and Accreditation	MHC	Major Histocompatibility Complex
CBMTG	Canadian Blood and Marrow Transplant Group	MICA	MHC Class I-Like Molecule, Chain A
CBB	Cord Blood Bank	MICB	MHC Class I-Like Molecule, Chain B
CBC	Congressional Black Caucus	MUD	Matched Unrelated Donor
CBS	Canadian Blood Service	NCBM	National Conference of Black Mayors
CBU	Cord Blood Unit	NIH	National Institutes of Health
CC	Collection Center	NIMS	National Incident Management System
CFU	Colony Forming Unit	NK	Natural Killer
CHTC	Certified Hematopoietic Transplant Coordinator	NMDP	National Marrow Donor Program
CIBMTR	Center for International Blood & Marrow Transplant Research	NRP	National Response Plan
CLIA	Clinical Laboratory Improvement Amendment	NST	Non-myeloablative Allogeneic Stem Cell Transplantation
CME	Continuing Medical Education	OCR/ICR	Optical Character Recognition/Intelligent Character Recognition
COG	Children’s Oncology Group	OIT	Office of Information Technology

csDSR	Cancer Data Standards Repository	OMB	Office of Management and Budget
CREG	Cross Reactive Groups	ONR	Office of Naval Research
CT	Confirmatory Testing	PBMC	Peripheral Blood Mononuclear Cells
CTA	Clinical Trial Application	PBSC	Peripheral Blood Stem Cell
CWD	Common and Well Documented	PCR	Polymerase Chain Reaction
DC	Donor Center	PSA	Public Service Announcement
DIY	Do it yourself	QC	Quality control
DKMS	Deutsche Knochenmarkspenderdatei	RCC	Renal Cell Carcinoma
DMSO	Dimethylsulphoxide	RCI BMT	Resource for Clinical Investigations in Blood and Marrow Transplantation
DNA	Deoxyribonucleic Acid	REAC/TS	Radiation Emergency Assistance Center/Training Site
DR	Disaster Recovery	RFP	Request for Proposal
D/R	Donor/Recipient	RFQ	Request for Quotation
EBMT	European Group for Blood and Marrow Transplantation	RITN	Radiation Injury Treatment Network
EM	Expectation Maximization	RT	Room Temperature
EMDIS	European Marrow Donor Information System	SBT	Sequence Based Typing
FBI	Federal Bureau of Investigation	SCTOD	Stem Cell Therapeutics Outcome Database
FDA	Food and Drug Administration	SG	Sample Group
Fst	Fixation Index	SSA	Search Strategy Advice
GETS	Government Emergency Telecommunications Service	SSP	Sequence Specific Primers
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)	SSOP	Sequence Specific Oligonucleotide Probes
GvHD	Graft vs Host Disease	STAR®	Search, Tracking and Registry
HHQ	Health History Questionnaire	TAT	Turn Around Time
HHS	Health and Human Services	TC	Transplant Center
HIPAA	Health Insurance Portability and Accountability Act	TED	Transplant Essential Data
HLA	Human Leukocyte Antigen	TNC	Total Nucleated Cell
HML	Histoimmunogenetics Mark-up Language	TSA	Transportation Security Agency

HR	High Resolution	URD	Unrelated Donor
HRSA	Health Resources and Services Administration	WGA	Whole-Genome Amplified
HSC	Hematopoietic Stem Cell	WMDA	World Marrow Donor Association
IBWC	Immunobiology Working Committee	WU	Work-up
ICRHER	International Consortium for Research on Health Effects of Radiation		